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Split Liver Transplantation

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Greater experience and improved outcomes in liver transplantation have necessarily led to longer waiting lists against a constantly limited donor pool. Split liver transplantation has been conceived as a means to increase the supply of liver grafts. The bipartition of a whole liver provides grafts for two recipients in a complex operation with equally complex manpower and logistical demands. The *in situ* technique of splitting offers advantages over the *ex vivo* technique, although after the time-dependent learning curve is overcome, they may theoretically be used interchangeably with acceptable outcomes. Aside from surgical expertise, donor characteristics and recipient pre-transplant status are risk factors for survival. This review will address the salient aspects of split liver transplantation, summarize the world experience with this procedure and describe the preliminary attempts in Asia. (*Asian J Surg* 2002; 25(4):285–90)

INTRODUCTION

The bipartition of a whole liver graft for use in two recipients has now become an accepted mode of increasing the supply of organs for transplantation. The universal donor shortage and the segmental anatomy of the liver form the basis for developing split liver transplantation (SLT). After the first case reported by Pichlmayr et al in 1989,[1] the procedure was performed in selected centres in Europe[2–4] and the United States,[5–7] but initial outcomes were not very encouraging. However, lessons learned from reduced size and living donor liver transplantation (LDLT) have paved the way for the renewed interest in SLT, especially because the problem of graft scarcity is persistent. A better understanding of liver anatomy, refinements in surgical technique and improved outcomes have led to a wider applicability of split liver grafting. While initially conceptualized to supply grafts for a paediatric and an adult recipient, it is now possible to divide the liver to generate grafts for two adult recipients.

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DONOR SELECTION

Essential in the success of SLT is the proper selection of a cadaveric liver graft to split, since not all donors are suitable for this procedure. Tissue injury may arise not only from the stress of cold ischaemia and reperfusion but from manipulation during dissection as well as parenchymal transection.

Certain donor characteristics make the liver graft ideal for splitting. The young haemodynamically stable potential organ donor with acceptable vasopressor support and a short hospital stay seems to be most suitable for a split procedure. Indeed, poor donor selection has been recognized as a cause of unfavourable outcomes, especially when both split grafts from the same donor fail.[8] Marginal donors are not suitable for splitting.[9] While the preference for younger donors has an obvious advantage, older ones who are stable with acceptable liver function may be considered. Donor age greater than 50 years has been considered a relative risk factor for poor outcome in liver transplantation[10] and there is a tendency to reserve graft splitting for donors younger than 50.[8] This arbitrary age limit has been challenged by Spada and colleagues from Italy who

have recently reported their experience in performing splits in donors older than 50 years.[11] Their results were favourable; survival rates were similar for recipients of split grafts from donors older than 50 compared to those receiving grafts from younger donors. Extension of the donor age limit for splitting is a way of expanding the donor pool.

An emerging donor source for SLT are recipients with familial amyloid polyneuropathy (FAP) whose liver explants may be used in another recipient in what is referred to as "domino liver transplantation". Livers from FAP patients are functionally and anatomically normal except for the production of an abnormal protein that is responsible for amyloid deposition.[12] FAP has a delayed clinical onset and a protracted course, making livers from patients with such metabolic defects suitable as allografts.

Domino whole organ liver transplantation using FAP liver grafts has been performed since 1995.[13] Domino SLT (splitting an FAP live donor liver for two recipients) has been reported from France[14] and two cases have been performed in Japan to date. SLT with grafts from a living donor would likely be a rarity and the logistical and organizational demands would be greater since the donor himself would likewise need a transplant from either a cadaveric or living donor, as was done in Japan. Using FAP livers for SLT would probably offer minimal addition to the donor pool, but is nevertheless a fundamentally sound alternative, especially in countries where the incidence of familial amyloidosis is high. Long-term follow-up results are awaited to determine the ultimate fate of such a graft in the recipient. Since the recipients are placed at risk for becoming symptomatic for the disease, this strategy should probably be limited to adult candidates.

Graft-Recipient Matching

The classical description of SLT consists of division of the liver along the umbilical fissure into the left lateral segment (segments II and III) and the right lobe together with the medial and caudate lobes (segments I, IV-VIII), based on the Couinaud classification.[15] This generates a graft for a small child and an adult or bigger child, respectively. With such a strategy, many centres have managed to significantly shorten waiting time and decrease waiting list mortality of paediatric candidates without compromising the adult donor pool.[16,17] It has been projected that splitting all cadaver donor livers in the USA could provide grafts for all the paediatric candidates in the entire country.[8]

Logically, the next step is to extend the application of SLT for two adult recipients. This would entail transection of the liver near the main lobar fissure to generate two hemiliver grafts. Aside from the technical difficulty of such a split procedure, a critical determinant in using split grafts from one liver for two adults would be size-matching between the graft and the recipient. From the accumulated experience in LDLT, it is now known that a partial liver graft that is 1% of the body weight,[18] or 40% of the computed standard liver weight,[19] of the recipient, is sufficient and associated with higher success rates. Similar size-matching criteria could be applied to SLT, provided that adequate selection of donor grafts to split is made. The decision-making is crucial since the urgent nature of the situation may not always permit doing adequate volumetric imaging studies prior to graft procurement as in LDLT. The surgeon would have to rely on weight estimates guided by formulae and make the final judgement of where to draw the partition line after actual inspection of the graft. SLT for two adult or adult-size recipients has long been contemplated by the pioneers of split liver grafting but only recently reported.[20,21]

Splitting Methods

Two methods of splitting a whole liver graft with respect to timing of cold perfusion have been described, the *ex vivo* and the *in situ* techniques. *Ex vivo*, also referred to as *ex situ* splitting, is done at the back table after conventional procurement and cold preservation of the whole liver graft. Emond et al and Broelsch et al from the University of Chicago were among the first to report on a series of *ex vivo* SLT,[5,6] which naturally evolved from reduced-size liver grafting in an effort to avoid graft wastage. In reduced-size liver transplantation, originally conceived for treatment of paediatric patients, only the left lateral segment was implanted and the right lobe was routinely discarded.[22,23]

The main disadvantage of *ex vivo* SLT is the prolonged ischaemia time due to a longer benching procedure. Some vital structures may be more difficult to identify and dissect in a pale bloodless graft and may predispose to anatomical complications in the recipient. Control of bleeders on the cut surface cannot be ensured. Back table

imaging techniques have been recommended to guide the transection of the parenchyma and hilar structures,[24,25] although this may not be necessary in all cases. Aside from the prolonged ischaemia time that may be detrimental to graft function,[26] bleeding from the cut surface and biliary problems are major concerns with this technique.

In situ splitting was then conceived to facilitate a more precise division of vital structures, especially the biliary tree, haemostasis of the cut surface and to shorten cold ischaemia time. With this technique, the liver is split in the heartbeating donor before cold preservation, following a procedure basically similar to that of graft procurement from a living donor. It requires a haemodynamically stable donor, a longer operation time and proper logistical arrangements with the donor hospital and other procurement teams. This innovation, which was first reported by Rogiers et al[27] and described in detail by Goss et al,[28] allows for more precise control of bleeding and bile leakage from the cut surface. Since minimal back table dissection is required, graft ischaemia time is shorter and this would be most favourable if the graft were to be transported to a distant recipient centre. The prevention of bleeding from the cut surface after revascularization saves on operating time and diminishes blood loss in the recipient. The main drawback is the prolonged procurement time and the inconvenience it may cause in the setting of multiorgan distant donor procurement. *In situ* splitting for two adult recipients would mean a larger transection area and consequently an even longer operating time. Although better-quality segmental grafts may be obtained, this procedure would probably be more practical for in-house cadaveric donors.

The combined *in situ*/*ex vivo* method has recently been described in order to maximize benefits from each approach in the least possible operating time. The procedure involves hilar dissection, partial transection of the parenchyma and division of the bile ducts after intraoperative cholangiography. This is followed by cold perfusion of the graft and completion of the bipartition on the back table.[29] On certain occasions, a planned *in situ* may be converted into a combination technique in donors who become haemodynamically unstable intraoperatively.

Clinical Outcomes

Attempts at SLT in the early 1990s yielded unfavourable results with survival rates in the range of 50%–60%.[3,6,7] Biliary complications as high as 40% were reported.[7] The poor outcomes were attributed to the pitfalls associated with the *ex vivo* splitting technique and the lack of familiarity with this procedure. Although the results were disappointing, they nevertheless demonstrated that it was technically feasible, with an enormous potential for increasing graft supply. Since there was clearly much room for improvement, several other transplant centres persisted in performing *ex vivo* liver splitting and subsequently published literature showed more promising results.[4,23,30,31] The introduction of the *in situ* technique in 1995 was met with much enthusiasm and led to more consistent graft and patient survival rates. Complications were notably diminished. Table 1 contrasts the published experience in *ex vivo* and *in situ* SLT over the last 5 years.[9,12,17,24–26,28,32–35]

Since *ex vivo* and *in situ* SLTs represent a technical evolution, it would be difficult to compare them per se. Only two centres have analyzed their own experience with each technique, with remarkably better outcomes with *in situ* splitting.[26,32] Nonetheless, comparable results with *ex vivo* splitting have likewise been demonstrated[17,33,35] and improved survival outcomes may be primarily related to experience and skill gained over time rather than the technique itself.[26] Obviously, other factors, especially the pretransplant status of the recipient, come into play. It is universally reported that high-urgency split liver graft recipients fare worse than elective ones. There has been a tendency to allot split liver grafts to candidates with relatively poor prognoses since such grafts were probably regarded as sub-standard. This may no longer be true with the greater expertise acquired by transplant teams. Properly obtained split liver grafts from selected donors may be just as good as whole organ transplants.

SLT: The Asian Experience

The serious lack of cadaveric donors in Asia mandates the quest for all means to increase the supply of allografts. LDLT has been largely resorted to in this part of the world, especially in Japan where cadaveric donation was practically absent until very recently.[36] SLT is a practical approach to extend the supply of a markedly limited donor pool. The Asian experience on SLT is still very limited, since there are not many donors available for splitting.

The first SLT in Asia was performed in 1997 at the Chang Gung Memorial Hospital in Kaohsiung, Taiwan.[37]

Table 1. Published experience on *ex vivo* and *in situ* SLT

Author	Year	*n*	Patient survival (%)	Graft survival (%)	Complications (*n*) Biliary	Vascular	PNF
EX VIVO							
Rogiers[32]	1996	19	63	58	3	0	0
Kalayoglu[33]	1996	12	92	75	2	1	0
Azoulay[25]	1996	27	79	78	6	4	1
Dunn[34]	1997	12	U 67 E 83	U 50 E 83	0	0	2
Mirza[9]	1998	24	78	68	3	2	1
Rela[35]	1998	41	90	88	6	4	0
Fawcett[17]	1998	28	93	78	4	3	0
Chardot[24]	1999	16	U 25 E 82	U 20 E 82	4	7	0
Reyes[26]	2000	25	74	61	2	4	3
IN SITU							
Rogiers[32]	1996	14	93	86	0	0	0
Goss[28]	1997	28	92	86	1	0	2
Reyes[26]	2000	29	96	81	1	3	2
Spada[11]	2000	39	89	89	13	6	1

PNF = primary non-function; U = urgent; E = elective.

Ex vivo splitting resulted in a left lateral segment graft that was given to a 3-year-old child with biliary atresia and an extended right lobe graft which was given to a 15-year-old, 57-kg female with Wilsonian cirrhosis. Subsequently, SLTs have been performed in Singapore, Korea, Japan, and Hong Kong in five major liver transplant centres. Until June 2000, a total of 26 SLTs from 13 donors have been performed in both adult and paediatric recipients, including adolescents who received right lobe grafts (Table 2). Twenty of them were primary transplants, while two were re-transplants for graft failure after LDLT. There were 15 male and 11 female recipients, 10 of whom were hospitalized prior to the transplant. The causes of end-stage liver disease or indications for transplantation are listed in Table 3. The first SLT from a living donor with FAP was done at the Kyoto University in July 1999 and the split hemihepatic grafts were given to recipients each weighing about 50 kg. The first cadaveric SLT for two adults was performed at the University of Hong Kong in January 2000. The results have been encouraging with a survival of 88% at a median follow-up time of 7 months.

Table 2. Cases of split liver transplantation in Asia, May 1997 to June 2000

Country	Number of liver grafts split	Adult-size recipients	Paediatric recipients	Alive
Taiwan	4*	3	4	5
Singapore	1	1	1	2
Korea	4	4	4	8
Japan	3	5	1	5
Hong Kong	1	3	0	3

*One right lobe split graft sent to Hong Kong.

Table 4 shows the complications in the recipients, the most common of which was bile leakage. Five patients required repeat laparotomy, while one required retransplantation for hepatic artery insufficiency, probably secondary to arcuate ligament syndrome. There was an equal incidence of complications in both *ex vivo* and *in situ* techniques. There were three mortalities, the first being in a child with portal vein stenosis and splenorenal shunting who developed refractory hypoxaemia after balloon dilatation of the portal vein and shunt embolization. Although portal flow improved, the patient eventually succumbed to respiratory failure. The other two mortalities were due to upper gastrointestinal bleeding and another to sepsis in a retransplant case. These last two patients

were ICU-bound prior to receiving a split liver graft.

The sharing of split liver grafts is a way to overcome the attendant logistical problems of SLT. Most liver transplant teams in Asia are small and may have limited resources and manpower to perform at least three operations sequentially or simultaneously. For a domino SLT with a living donor for the FAP patient donating split grafts, four operations will have to be scheduled. One way of maximizing the use of split grafts is to share between centres within or between countries. This is already being practised widely in Europe.[25,31,35,38–40] In Asia, sharing between transplant centres within countries, one in Taiwan (between the Kaohsiung Chang Gung Memorial Hospital and National Taiwan University) and another in Japan (between Kyoto University and Shinshu University) has taken place. International sharing of split liver grafts took place between Taiwan and Hong Kong in January 1999.[41] Singapore and Hong Kong have a standing reciprocal agreement to share split liver grafts but have not had the occasion to do so. The establishment of a centralized referral centre and mutual agreements among participating transplant units that meet criteria for joining the interchange would be essential for such endeavours.

Table 3. Underlying diseases of split liver graft recipients in Asia

Diagnosis	No. of patients
Biliary atresia	8
Hepatitis B cirrhosis	6
Graft failure after LDLT for biliary atresia	2
Hepatitis C cirrhosis	2
Wilson's disease	2
Primary sclerosing cholangitis	2
Primary biliary cirrhosis	1
Haemangioendothelioma	1
Oxalosis	1
Familial amyloidosis	1

LDLT = living donor liver transplantation.

Table 4. Complications in split liver transplant recipients in Asia

Complication	No. of patients
Bile leakage	4
Segment IV necrosis in extended right lobe grafts	2
Portal vein stenosis with SR shunting	1
Portal vein thrombosis	1
Hepatic artery insufficiency R/O arcuate ligament syndrome	1
Intra-abdominal haemorrhage/abscess	1
Upper gastrointestinal bleeding	1
T-tube dislodgement	1

SR = splenorenal.

CONCLUSION

SLT is an attractive and practical way to meet the supply-and-demand problem in organ transplantation. With the learning curves in this mode of liver replacement being overcome, survival rates now parallel that of whole organ liver transplantation. Indeed, the search for more sophisticated means to increase graft supply may only be justified once the potential of SLT has been fully exploited. While greater experience has been acquired and improvements in clinical outcomes have been achieved, SLT nevertheless remains a formidable surgical procedure, which is reserved for transplant teams with extensive experience in liver resections and transplantation of both cadaveric and live donor grafts. It requires not only the ability to perform the operation but to solve problems and complications peculiar to this type of transplant. Expertise gained in *ex vivo* and *in situ* splitting will allow flexibility in opting for whichever is most convenient for a given circumstance. Aside from technical expertise, donor selection and graft allocation based on adequate size matching are important determinants of success.

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